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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,486	11/29/2000	Takchiro Yatomi	1110-0280P	1332

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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/701,486	Applicant(s) YATOMI, TAKEHIRO	
	Examiner Zachariah Lucas	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-7* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

1. Claims 1, and 4-7 are pending in this application. Claim 4 has been withdrawn as drawn to a non-elected invention, and claims 1, 3, and 5-7 were rejected in the Final Action mailed on October 1, 2002 (the prior action). In the After Final response filed on December 31, 2002 (the Response), claim 3 was cancelled from the application, and claim 1 was amended. This action is in response to an RCE filed on March 17, 2003 (the RCE). Claims 1 and 4-7 are pending, and claims 1 and 5-7 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **(Prior Rejection- Withdrawn)** Claims 1, 6, and 7 were rejected in the previous office action for containing subject matter that was not described in the specification sufficiently to show that the applicant had possession of the claimed invention when the application was filed. In view of the Applicant's amendment of the claims limiting them to embodiments wherein the Fas antagonists inhibit Fas/Fas ligand binding, the rejection is withdrawn.

4. **(New Rejection)** Claims 1, and 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an autoimmune demyelinating disease using anti-Fas ligand antibodies, does not reasonably provide enablement for methods of treating any such disease using any Fas antagonist that blocks Fas-Fas ligand binding and therefore suppresses apoptosis. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the claimed invention. As described above, the claims read on methods of treating autoimmune demyelinating diseases by inhibiting apoptosis of using any Fas antagonist that inhibits Fas-Fas ligand binding. Also as indicated above, an autoimmune disease is generally understood to be a disease arising when a body's immune cells, or antibodies therefrom, attack other bodily cells.

In the RCE, the applicant presents two alternative associations between Fas-Fas ligand induced apoptosis, and demyelinating diseases. In the first, a direct association, the disease is caused by apoptosis of cells in the myelin sheath. However, in such a case, there is no apparent cause of the disease that may be classified as "autoimmune" as it is a signal factor malfunction, rather than immune cells, that cause the damage. In the second association, the disease is caused by an autoimmune attack of myelin cells by T or B cells of the immune system. The disease in this situation results from a malfunction in the autoimmune system wherein the self-reactive cells were not killed through Fas induced apoptosis as they should have. This second case is an autoimmune disease, but it is a suppression of Fas induced apoptosis that lead to the problem, and it is not likely that suppressing apoptosis would be an effective treatment for these disorders.

There is support for the Applicant's assertions in the references of record. However, the art addressing the treatment of autoimmune demyelination also support the Examiner's conclusion that suppression of apoptosis would not be effective in the treatment of autoimmune demyelination. See, e.g. Chu et al., U.S. Patent 6,544,523. Chu teaches a method of treating autoimmune diseases, including autoimmune demyelinating diseases, of which multiple sclerosis is a named example. Col. 10, line 37 to col. 11, line 29. The reference teaches that autoimmune diseases are diseases resulting from situations comparable to the second scenario presented by the Applicant. Col. 10, lines 42-45. Chu teaches that in this case, the administration of Fas ligand to the affected areas, thereby causing apoptosis, and not inhibiting it, would be an effective treatment. Col. 12, lines 2-12, and col. 31, lines 14-22. In view of the fact that autoimmune induced multiple sclerosis would appear to be treatable by inducing apoptosis, the Applicant has not enabled the presently claimed method of treating such diseases by suppressing it.

In presenting these two possible associations, the Applicant has argued that the administration of a Fas antagonist could have two opposite effects depending on the cause of the demyelinating disease being treated. In the Response of December 321, 2002, the Applicant stated: "The unpredictability of the field precludes the inference made by the Examiner that it would be obvious to treat MS using a Fas antagonist." Id, page 4. Thus, the Applicant themselves have stated that, due to the unpredictability of the field, one skilled in the art would not know whether to inhibit or induce apoptosis to treat MS.

In view of this, and the absence of any teachings in the application's disclosure to demonstrate that the direct Fas association (induce apoptosis), as opposed to the indirect Fas association (failure to induce apoptosis in T-cells), was indeed the source of Fas pathology. The

Applicant has present no better evidence than the references of the prior art, including and especially Elliott. Only a single working example was presented in the application: the use of anti-Fas ligand antibodies. In view of the contradictory teachings in the art, although one skilled in the art would have had an indication that Fas inhibition may be effective, the applicant's showings would not have enabled one of ordinary skill in the art to practice the claimed invention using any Fas-antagonist, and against any form of autoimmune demyelinating diseases.

However, while the applicant is not enabled for the full scope of the claimed method of treating an autoimmune demyelinating disease, the application does present evidence, in an accepted animal model of MS, that administration of an anti-Fas ligand antibody was effective in treating the disease. Because of the uncertainty regarding the claimed invention as described above, and the lack of any demonstration as to why the animal model worked, the Applicant is not enabled for the full scope of the method as identified by claim 1. However, the Examiner submits that the Applicant is enabled to the extent of the teachings of the examples in the specification.

Claim Rejections - 35 USC § 102

5. **(Prior Rejection- Withdrawn)** Claims 1, 6, and 7 were rejected in the prior actions under 35 U.S.C. 102(e) as being anticipated by Us Patent Number 6,399,327, issued to Wallach et al. (Wallach). These claims describe a method of treating autoimmune demyelinating diseases, including MS by administering a Fas antagonist. In making the rejection, the Examiner interpreted Fas ligand as being any molecule that binds to the Fas receptor and thereby inhibits

the Fas-ligand induced apoptosis. In the Response, the Applicant amended claim 1 such that it is limited to Fas antagonists that inhibit Fas-Fas ligand binding. In the RCE, the Applicant states that the MORT-1 protein, an intracellular ligand to Fas whose binding is inhibited in Wallach to prevent apoptosis, would not be considered to be the Fas ligand of claim 5. In view of the Amendment and the arguments presented by the Applicant, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

6. **(Prior Rejection –Withdrawn)** Claims 1-3 and 7 were rejected in the prior action under 35 U.S.C. 103(a) as being obvious over Keana et al., U.S. Patent Number 6,184,210. Claims 2 and 3 are no longer pending in the application. Claim 1 has been amended such that it is now limited to Fas antagonists which suppress apoptosis by inhibiting Fas/Fas ligand binding. As pointed out by the applicant, Keana does not teach the inhibition of Fas/Fas ligand binding. As such, Keana is no longer applicable as prior art against the claims without additional teachings.

7. **(Prior Rejection – Withdrawn)** Claims 1-3, 6, and 7 were rejected under 35 U.S.C. 103(a) as being obvious over Hughes and Crispe, J. Exp. Med, Vol. 182, 1395-1401, (1995) (Hughes); in view of Holoshitz et al, U.S. Patent Number 6,098,631; and D'Souza et al., J. Exp. Med., vol. 184, pp. 2361-70 (1996) (D'Souza). Claims 1-3 describe a method of inhibiting an autoimmune demyelinating disease using a Fas antagonist that suppresses Fas-Fas ligand binding and apoptosis. The applicant has traversed the rejection by arguing that Holoshitz does not teach a method of treating MS, and that the purpose of the method of Holoshitz is to induce apoptosis, and that D'Souza teaches away from the involvement of Fas-Fas ligand interactions with MS.

Although the Examiner disagrees with the Applicant's description of D'Souza (as described below), this rejection is hereby withdrawn.

8. **(Prior Rejection – Reformed and Maintained)** Claims 1-3, 5, and 6 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lynch et al. in U.S. Patent Number 5,830,469 in view of D'Souza. This rejection is reformed as follows:

Claims 1 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of D'Souza, and Wallach et al., U.S. Patent 6,399,327, and further in view of Lynch. The claims have been described above. The applicant traversed the previous rejection involving D'Souza on the grounds that D'Souza teaches away from the use of Fas-inhibitors to treat MS, and that Lynch does not teach the use of anti-Fas ligand antibodies to treat MS.

The examiner disagrees with the applicant's assertion that D'Souza teaches away from the inhibition of the Fas pathway to treat MS. D'Souza teaches that the Fas-Fas ligand pathway are involved in the loss of the myelin sheath in the CNS leading to MS. See, pp. 2367-2368. The applicant's argument that D'Souza teaches away from the involvement of the Fas- Fas ligand in MS is unfounded. The reference actually teaches that the part played by those compounds may not be that of causing apoptosis, but of causing some other dysfunction in the cells that still leads to the demyelination of the cells. P. 2367, col. 2. Thus, D'Souza teaches that even if the Fas pathway does not cause cell apoptosis, it is nonetheless involved in the development of MS, and therefore a target for treatment.

This teaching is highlighted by the suggestion in the last paragraph of D'Souza, stating that "the availability of soluble fas, neutralizing antibodies to fas or fas ligand, or inhibitors of

fas ligand induction or fas-mediated cell death provides potential means to manipulate this signaling pathway for therapeutic applications to MS." Thus, D'Souza does not indicate that Fas in uninvolved, but merely questions the form of involvement of that the Fas pathway takes, and then indicates that Fas/Fas ligand inhibitors are likely to be useful for the treatment of MS.

The suggestion of D'Souza that MS may be treatable with a Fas-ligand inhibiting compositions is supported by the teachings of Wallach. As described in the prior action, Wallach teaches the inhibition of the Fas pathway for the treatment of autoimmune diseases. Wallach, columns18-19, and 24, lines 16-45. In the paragraph spanning from column 18 to column 19, Wallach states that one utility of the products taught therein is "to inhibit the Fas-ligand-effect." The reference also states, in column 24, that among the disorders such inhibitors would be useful in treating is the "death of oligodendrocytes in the brain in multiple sclerosis." Each of D'Souza and Wallach therefore teach an association between Fas-ligand induced cell death, no matter the operation of the cell death, and the use of Fas-ligand inhibitors to treat the disease.

The Lynch reference teaches that inhibitors of Fas/Fas ligand interactions are useful for the inhibition of Fas-induced apoptosis, caused by the interaction between Fas and its ligand. Although the reference does not teach the use of such inhibitors to treat MS in specific, the reference does teach their use in the treatment of Fas pathway associated diseases. Thus, this reference, in combination with D'Souza and Wallach, which teach that MS is such a disease, demonstrate the claimed method would have been obvious to one of ordinary skill in the art. The references teach a method of administering a Fas/Fas ligand binding inhibitor to a population suffering from MS.

It is noted that the claims require the suppression of apoptosis, and that the references do not indicate that Fas-induced apoptosis is the cause of MS. However, the references do teach the administration of the same material to the same population. Because the references teach all other aspects of the claim except the form of cell death to be suppressed (i.e. the result of the method), the effect that the administration would have had on the recipient of the treatment would be identical. The form of cell death is not dispositive of the applicability of the references against the claimed method.

Applicant's arguments that, given the disparity in the art as to the pathology of MS, one of ordinary skill in the art would not have had a reasonable expectation of success is noted. However, D'Souza also teaches the increased targeting of the oligodendritic cells by T-cells in MS. Page 2368. The reference also speculates as to an association between the T-cell targeting of the cells, and the Fas induced cell death. Thus, the reference suggests the potential for a relationship between the two MS pathologies, and indicates that the authors of the reference, in suggesting the use of Fas inhibitors for the treatment of MS, were aware of the conflicting art. In view of these additional teachings over the primary teachings of the direct Fas related pathology of MS, one skilled in the art would have had a sufficient reason to expect that inhibition of the Fas pathway in MS oligodendrites would be an effective method of treating MS as indicated by D'Souza and Wallach.

9. **(Prior Rejection –Withdrawn)** Claims 1, 3, 5, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keana as described above or over Hughes in view of Holoshitz and D'Souza as described above; and either of those sets of references further in view

of Nagata. In view of the Withdrawal of the rejections over Keana and over Hughes, D'Souza, and Holoshitz, this rejection is also hereby withdrawn.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
May 30, 2003

JAMES HOUSEL 6/1/03
SUPERVISORY PATENT EXAMINER
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